order to demonstrate their inapplicability to the present, newly-added claims 82-128. Each of the rejections is addressed individually below.

Lack of Written Description under 35 USC § 112, ¶ 1

Claims 41-53 in the existing case were rejected for lack of written description of the following phrases:

(i) "a ***library*** of test compounds";

(ii) "providing a ***library*** of test compounds ***to be assayed for effects on a biological process in the cells***, wherein the biological process is characterized in that ***production of an intracellular product indicates activity of the process***";

(iii) "***introducing the cells and test compounds*** into the plurality of reaction vessels, wherein ***each reaction vessel contains a subset of the library of test compounds***";

(iv) "contacting the test compounds with the cells for a period of time and ***under conditions sufficient for the test compounds to exert an effect on the biological process so that the levels of the intracellular product are affected***";

(v) "***washing away unbound ligands***";

(vi) "wherein in the step of introducing the cells and the test compounds into the plurality of reaction vessels, ***each reaction vessel contains an average of one test compound from the library of test compounds***";

(vii) "wherein the step of measuring comprises measuring levels of ligand which bound to the biological component ***by measuring levels of photo emissions***"; and

(viii) "wherein before the step of measuring, ***the method further comprises introducing a second ligand that binds specifically to the ligand and washing away unbound ligands and wherein the step of measuring comprises measuring levels of the second ligand***".

The cited language is not present in the currently-pending claims, thereby obviating the stated rejection. Support for the language of the new claims can be found throughout the specification.

Specifically, support for newly added claim 82 can be found *inter alia* in original claim 1 and throughout the specification, for instance, in the Examples found on pages 48-110 of the specification. With respect to the ligand, the term "associate with" is defined in the paragraph bridging pages 23 and 24 of the specification.

Claim 83 is drawn to a method of screening test compounds for establishing their functional fingerprint. Support for such language can be found on page 41 line 22 through page 42 line 14, as well as in Example 12 on page 97-98 and Figure 13.

Claim 84 specifies that unassociated ligand may be removed from each reaction vessel. Support for such language can be found throughout the Examples in the teaching that antibody solution (*i.e.*, ligand solution) is aspirated off prior to detection (see, for example, page 56 lines 7-8 of the specification).

Support for claim 85 can be found on page 24 lines 8-19 where it is recited that a biological component may be any detectable compound or portion of a compound that (i) is found in a cell; (ii) participates in one or more biological reactions; and/or (iii) is produced by one or more biological reactions. Page 25 lines 6-7 reads: "Typically, but not necessarily the detection target will be a product of or a participant in the reaction being studied". Additional support can also be found on page 6 lines 17-22 of the specification, where it is recited that, in certain preferred embodiments, the invention provides a screening method for identifying compounds capable of affecting a biological or chemical process by detecting levels of component in the biological or chemical process (*i.e.*, a component that participates in the chemical or biological process) or resulting from the biological or chemical process (*i.e.*, the component is a product of the chemical or biological process).

Support for claims 86-93 can be found, for example, in the paragraph starting on page 5 line 17 and ending on page 6 line 5, in the section entitled "Detection" on pages 35-38, and throughout the Examples, where it is recited that the biological component(s) is (are) detected by means of its (their) interaction with a binding partner ligand, that the binding may be specific, and that in certain embodiments, the binding partner ligand is an antibody and may include a peroxidase, for example horseradish peroxidase (HRP). The specification also specifies that detection of the biological component may be accomplished by a two-step binding procedure using an antibody (first ligand) and a secondary antibody (secondary ligand) conjugated to the

enzyme horseradish peroxidase (see, for example, page 10 lines 13-17). Claims 89 and 90 specify that detection of the bound secondary ligand may be performed while the bound secondary ligand is inside the cell (*e.g.*, without requiring cell lysis). Support for such language can be found throughout the Examples in the teaching that the bound secondary ligand (*e.g.*, antibody conjugated to horseradish peroxidase) is detected in intact cells.

Claims 94 and 95 recite elements pertaining to detection methods (support for which can be found on page 37 lines 3-12 and on page 38 lines 13-23).

Claim 96 specifies that the cells may be introduced into the reaction vessels so that they adhere to the reaction vessels surface. Support for such language can be found, for example, in the description of Figure 6 on page 10 lines 20-24 of the specification, in which an immunodetection assay using varying densities of *adherent* HeLa cells is described.

Claims 97-100 include the use of one or more assay solutions containing a reagent for detecting the presence or amount of a biological component (detection target). Support for such language can be found on page 6 lines 17-22. Further support is provided in Figure 5 and Example 4 (pages 56-58) where it is described that the reagent (*e.g.*, trapoxin A) may exert an effect on the intracellular biological or chemical process of interest (*e.g.*, protein phosphorylation). Additional support can be found on page 31 lines 1-12, in Figures 1-4, 8, 11c-d and in Examples 1-3, 6-7 (pages 48-63), where it is recited that the reagent (*e.g.*, BrdU) may be incorporated in the biological component resulting from the intracellular biological or chemical process of interest (*e.g.*, DNA synthesis).

Claim 101 includes covalent modifications of intracellular components as markers for detecting the effects of test compounds on intracellular biological and chemical processes. Support for this language can be found throughout the specification, particularly on page 31 lines 23-24 and page 32 lines 1-15, which recite the detection of covalent modifications (*e.g.*, phosphorylation or acetylation) to identify test compounds capable of affecting various cellular functions.

Claims 102 and 103 recite intracellular biological reactions as examples of covalent modification of intracellular components, support for which can be found *inter alia* in original claim 9.

Support for newly added claims 104 and 105 can be found on page 56 lines 23-23 and page 96 lines 11-13, in which it is recited that in certain embodiments that compounds can be screened for their effect on post-translational events. It is well recognized in the art that the cellular processes listed on page 42 lines 9-13 are post-translational events.

Claim 106 specifies that the ligand interacts with the post-translationally modified intracellular component (*i.e.*, a biological component product of a post-translational biological process). Support for this language can be found, for example, on page 24 lines 8-19, page 25 lines 6-7 and page 6 lines 17-22 as detailed above for claim 85. Additional support can be found, for example, in Example 4 (pages 56-58 of the specification) in the teachings that an antibody (*i.e.*, ligand) can be used to detect the presence of phosphorylated nucleolin or histone H3 in the cells.

Support for claim 107 can be found throughout the specification, for example on page 42 lines 7-14, in the teachings that compounds can be screened for their ability to effect a variety of cellular processes, including "protein concentration, phosphorylation, methylation, acetylation, lipidation, isoprenylation, ubiquitination".

Claims 108 and 109 specify that the cells used in the screening method of the invention may be from the same or different cell-lines. Support for such language can be found, for example, on page 30 lines 1-4 of the specification where it is recited that a variety of cell-types can be used. Additional support can be found throughout the Examples, for instance, in Examples 1-3 on pages 48-56 which teach the use of the invention with a single cell line (Mv1Lu mink lung cells) for studying changes in DNA synthesis.

Claims 110, 111 and 112 find support *inter alia* in original claims 6, 7 and 8, respectively.

Claims 113-115 find support *inter alia* in original claims 31-33 and throughout the specification, for example, in the section entitled "Test Compounds" found on pages 39-40 of the specification, where it is recited that compounds may be obtained from natural or synthetic sources. The specification specifies that the compounds may be from a combinatorial library and that when compounds are attached to a solid support, the compounds may be delivered to the reaction vessel in association with the support, and be released from a support inside the vessel. With respect to the term "combinatorial library", one skilled in the art will appreciate that

Applicant means a collection of compounds obtained from combinatorial synthesis, as discussed on page 25 lines 10-14 of the specification.

Claims 116-126 recite elements pertaining to the assay format. Specifically, claims 116-119, which include elements pertaining to the volume of the reaction vessels of the assay format, find support *inter alia* in original claims 14-17 and on page 6 lines 6-16; Claims 120-123, which are drawn to elements regarding the spacing of the reaction vessels of the inventive assay, find support on page 5 lines 3-9 and page 29 lines 1-5; Finally, claims 124-126, which provide recitation of elements relative to the reaction vessel density of the assay used in the invention, find support, for example, in Examples 1-3 found on pages 48-56, in the teachings that a 384-, 1536- or 6144-well plate can be used to practice the invention. A person of ordinary skill in the art would appreciate that the dimension of standard 384-, 1536- or 6144-well plates used in the art is approximately 128×86 mm^2.

Claim 127 specifies that the test compounds introduced in each of the reaction vessels may be the same or different. Support for such language can be found throughout the specification. For instance, Example 10 on page 65 and corresponding Figure 11 describe an experiment where several purine analogs were screened for their activity as suppressors of G2-arresting agents: the test compounds are the same across a row of reaction vessels, but are different going down a column.

Claim 128 specifies that each reaction vessel may contain one test compound. Support for such language can be found, for example, on page 86 lines 15-17 where it is recited that compounds from certain libraries were pooled at two compounds per well, while compounds from other libraries were tested *singly* (*i.e.*, one compound per well).

Applicant respectfully submits that addition of the claims, as described above and detailed herein, does not present new matter, and Applicant thus respectfully requests entry of these additions, and consideration of these additions in the following remarks.

Lack of enablement under 35 U.S.C. § 112, ¶ 1

Claims 41-51 and 53 in the existing case were rejected for lack of enabling written description for a method for screening ***all*** libraries of ***all*** test compounds with effects on ***all***

biological processes in ***all*** cells, comprising the steps of... providing a plurality of ***all*** cells; providing ***all*** libraries of ***all*** test compounds to be assayed for ***all*** biological processes in ***all*** cells, wherein ***all*** biological processes are characterized in that production of ***all*** intracellular products indicate activities of ***all*** of the aforementioned processes... wherein each reaction vessel contains ***a/all*** subset(s) of ***all*** libraries of ***all*** test compounds, contacting ***all*** test compounds with ***all*** cells for ***all*** periods of time and under ***all*** conditions sufficient for ***all*** test compounds to exert an effect on ***all*** biological processes so that ***all*** levels of ***all*** intracellular products are affected, introducing into each reaction vessel ***all*** ligands that bind specifically ***all*** intracellular products in ***all*** biological processes so that ***all*** ligands bind to ***all*** products..., etc. However, it was conceded that the claims were enabling for "screening strategies associated with the following different classes of chemical compounds as affecting aspects of the cell cycle, as indicated by these examples from the instant specification:" citing Examples 6, 7, 9, 10 and 11.

Applicant respectfully submits that the specification ***does*** reasonably provide enablement commensurate with the scope of the presently claimed invention, and submits that the specification provides sufficient guidance for one of ordinary skill in the art to make and use the invention without undue experimentation.

The standard for enablement is based on the determination of whether the disclosure contains sufficient information regarding the subject matter of the claim as to enable one skilled in the art to make and use the claimed invention. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied (MPEP 2164.01(b)). Applicant is not required to disclose every operable species, but only representative examples, with enough teaching and guidance so as to enable a person of ordinary skill in the art to practice the invention without undue experimentation.

Applicant respectfully submits that the specification ***does*** provide sufficient guidance and ***does*** teach one of ordinary skill in the art how to screen test compounds capable of exerting an effect on intracellular biological or chemical processes, ***without undue experimentation***. Specifically, Applicant claims a method for screening compounds, said method comprising:

a. introducing into each of a plurality of reaction vessels:

a plurality of cells; and

one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated;

Applicant asserts that there is no undue experimentation in introducing the cells and the test compounds in each of the plurality of reaction vessels. The methods needed to perform the step of introducing the cells and/or the test compounds in the reaction vessels were well-known in the art at the time the invention was made and readily available to a person of ordinary skill in the art. Applicant provided ample teaching of methods suitable to carry out this step. Specifically, in describing a method of practicing the screening method of the invention, Applicant teaches the use of plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL; Corning Costar, Corning, NY) or 1536 (Greiner America, Lake Mary, FL) wells, which were commercially available at the time the invention was made (see p. 29 lines 6-19). Applicant further discloses that denser plates, such as the 6144 well plates described by You *et al.* (*Chem. Biol.* 4:969-975. 1997; U.S.S.N.# 09/184,449 entitled "Casting of Nanowell Plates") are particularly preferred for practicing the invention, and that an ideal assay for high throughput screening would be compatible with any or all of the above-mentioned array formats. The reaction vessel assay formats needed to practice the invention were well-known in the art at the time the invention was made, and were readily available to the person of ordinary skill in the art who would want to make or use the invention.

In addition, Applicant describes the use of a variety of cell types that can be grown or delivered at the bottom of the plurality of reaction vessels described in the present invention, and probed for a specific biological component (*e.g.*, detection target) produced by an intracellular biological or chemical process of interest. Any cells can be used, including, for example, bacterial cells, yeast cells, plant cells, insect cells or animal cells (see page 30 lines 1-4). As stated on page 48 lines 9-11, the invention does not require the use of (but *can* use) engineered cell lines, which means that a wide range of cells including both primary and transformed cells (*i.e.*, cells that were not derived from a cancer but were produced by laboratory treatment of normal cells) of any tissue type or genetic background can be used (see page 48 lines 10-11). As seen in the Examples and Figures provided, they can include Mv1Lu and 6F mink lung epithelial

cells (Figures 2-4, 6a, 7 and 8a-b), A549 human lung carcinoma cells (Figures 5, 6b-c 11b and 11e), HeLa human cervical carcinoma cells (Figures 6c and 11c-d), and mouse embryonic stem cells (Figure 8c).

Furthermore, Applicant describes the use of a wide variety of test compounds that could be screened according to the method of the invention. Applicant teaches that the present invention may be practiced with test compounds obtained from natural or synthetic sources. General descriptions and references of libraries of natural and synthetic compounds are found in the specification on pages 39-40. Applicant specifies that, traditionally, the source of test compounds for use in biological assays has been extracts containing natural products. Applicant also points out that the advent of combinatorial chemistry and split-pool synthesis now adds to this repertoire complex "natural-product-like" libraries, the products of laboratory syntheses, as a source of small molecules to be screened for novel compounds with biological activity. One of ordinary skill in the art will be aware of other collections of test compounds that can be isolated from natural sources or synthesized using methods known in the art.

In addition, Applicant has provided ample teaching in the specification, particularly in the Examples, of experimental conditions suitable for test compounds, when contacted with various cells, to exert an effect on a variety of intracellular biological or chemical processes including, but not limited to, gene expression, DNA synthesis, protein acetylation, protein phosphorylation, cell growth and mitosis (see Examples 1-14 on pages 48-105). Applicant is not required to disclose every operable species, but only representative examples. Thus, the scope of the claimed invention is not limited to the recited examples, but encompasses any intracellular biological or chemical process known in the art, that can be probed using the present invention. One skilled in the art can use and apply the teachings of the invention to screen compounds to identify those compounds that affect intracellular biological or chemical processes other than those disclosed in the present invention.

While the examples in the specification teach the use of several types of cell-lines and classes of compounds in the present invention, the scope of the invention is not limited to screening only those compounds in those cell types described in the Examples. Those of ordinary skill in the art would be aware of a wide variety of cells that are known in the art and available to practice the invention, as well as test compound(s) that can be obtained, for example,

through synthetic methods or isolated from natural or biological sources. One practicing the invention would choose a biological system (*e.g.*, cell) of interest to them from a number of cells, and would select a collection of test compounds from a synthetic or natural source, and assay the compounds according to Applicant's screening method. Applicant submits that the specification provides sufficient guidance and teaching to enable one of ordinary skill in the art to practice the invention to the full scope of the claims, and asserts that the step of introducing a plurality of cells and one or more test compounds in each of a plurality of reaction vessels cannot rise to the level of undue experimentation.

b. introducing into each of the reaction vessels a first ligand characterized by an ability to associate intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process;

The methods needed to perform the step of introducing the ligand in the reaction vessels were well-known in the art at the time the invention was made. Applicant has provided ample teaching in the specification, particularly in the Examples, of methods suitable to carry out this step. In addition, Applicant teaches throughout the Examples experimental conditions suitable for the ligand to associate with a target biological component (*e.g.*, detection target) intracellularly. The term "associate with" is defined in the paragraph bridging pages 23 and 24. While the Examples in the specification teach the use of several types of ligands, the scope of the invention is not limited to using only those ligands as detecting agents. Applicant teaches the general characteristics of suitable ligands to be used in the present invention on pages 26 and 27 of the specification (see also the paragraph starting on page 35 line 19 and ending on page 36 line 16). Furthermore, those of ordinary skill in the art would be aware of a wide variety of ligands and established specific associations that are known in the art. One practicing the invention would choose a chemical or biological process of interest to them from a number of different chemical or biological processes which could be assayed for, and would select a ligand suitable for detecting the biological target; therefore a practitioner will not be at a loss as to how to perform the assay. Applicant submits that the specification provides sufficient guidance and teaching to enable one of ordinary skill in the art to practice the invention to the full scope of the claims.

c. assaying for ligand-component association in the reaction vessels

Applicant respectfully submits that there is no undue experimentation in assaying for ligand-component association. Specifically, Applicant teaches detection methods suitable for carrying out this step in the specification on pages 37-38 and throughout the Examples.

Additionally, Applicant would like to point out that, although the specific application of the claimed method using different test compounds, cell-lines or ligands other than those described in the application might involve some experimentation, the enablement requirement is still satisfied since the amount of experimentation would not be undue. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue'."). As the Federal Circuit explained in *Genetech v. Novo Nordisk*, "undue experimentation" refers to the failure to disclose "any specific starting material or of any of the conditions under which a process can be carried out." *Genentech v. Novo Nordisk*, 42 USPQ2d 1001 (Fed. Cir. 1997). For example, as detailed above and as recited from the specification, Applicant has provided sufficient guidance to the worker of ordinary skill in the art to obtain a variety of test compounds from synthetic or natural sources, to obtain a variety of cells (whether they be primary and transformed cells, from any tissue type or genetic background), to obtain a suitable ligand as detecting agent, and to screen the test compounds for their ability to exert an effect on an intracellular biological or chemical process of interest, and thus has provided specific starting materials (*e.g.*, test compounds, cells and ligands) and conditions under which the test compounds ability to affect cellular processes can be assessed.

In summary, Applicant asserts that the newly added claims are fully supported and enabled by the specification. The specification provides sufficient guidance and teaching to enable one of ordinary skill in the art to practice the invention commensurate in scope with the claims. Applicant respectfully submits that the present application contains a complete written description of the presently claimed invention.

Obviousness over:

1) Gall p *et al.* (USP 5,525,734; "Gallop"), Manns (USP 4,948,442; "Manns"), page 29, lines 6-19 of the present application, and Craig ("Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt eds., Washington D.C.: American Chemical Society, 1997; "Craig");

2) Zambias *et al.* (USP 5,736,412; "Zambias"), Manns, page 29, lines 6-19 of the present application, and Craig; and

3) Godowski *et al.* (USP 6,025,145; "Godowski"), Manns, page 29, lines 6-19 of the present application, and Craig.

Several claims in the existing application were rejected for obviousness over 1) Gallop, Manns, page 29 lines 6-19 of the parent application and Craig; 2) Zambias, Manns, page 29 lines 6-19 of the parent application and Craig; and 3) Godowski, Manns, page 29 lines 6-19 of the parent application and Craig.

Gallop was cited as teaching methods of synthesizing and screening pyrrolidine compound libraries on solid supports, as well as teaching methods of screening the library for biological or pharmaceutical activity. However, it was conceded that Gallop does not suggest or teach a method of screening compounds where the volume of each reaction vessel is less than or equal to approximately 200 microliters. In addition, Applicant submits that there is no indication or teaching in Gallop of the use of a cell-based assay for performing the biological assay. Furthermore, Gallop does not teach the ability of the compounds to exert an effect on intracellular processes as a basis for the biological screen, and that this effect may be detected via a ligand (or combination of ligands) that associates with the target biological component ***inside the cell.***

Zambias was cited as teaching a method of synthesizing an (m x n) array of different chemical compounds wherein each of the compounds has at least one structural diversity element selected from a group of amines and ketones and wherein the scaffold structure is selected from a group consisting of aminimide, imidazolone, sulfonylaminimide and phosphonylaminimide (see abstract of Zambias). Zambias was also cited as teaching simultaneous screens for assaying large numbers of parallel compound samples for exploring biological activity. However, it was

conceded that Zambias does not suggest or teach a method of screening compounds where the volume of each reaction vessel is less than or equal to approximately 200 microliters. In addition, Applicant submits that there is no indication or teaching in Zambias of the use of a cell-based assay for performing the biological assay. Furthermore, Zambias does not teach the ability of the compounds to exert an effect on intracellular processes as a basis for the biological screen, and that this effect may be detected via a ligand (or combination of ligands) that associates with the target biological component ***inside the cell***.

Godowski was cited as teaching a kinase receptor activation (KIRA) assay for measuring autophosphorylation of a tyrosine kinase receptor of interest. Godowski's method involves contacting cells with a compound to assay the ability of the compound to affect activation of the auto-phosphorylation process. After the cells are exposed to the compound, the cells are lysed. The lysate is removed and transferred to a second solid phase containing a capture agent which binds specifically to the tyrosine kinase receptor. The second solid phase is washed to remove unbound cell lysate, leaving the captured receptor. The captured tyrosine kinase receptor is then contacted with anti-phosphotyrosine antibodies (*e.g.*, detecting ligand) which are specific to phosphorylated residues and the levels of the antibodies are measured. However, it was conceded that Godowski does not suggest or teach a method of screening compounds where the volume of each reaction vessel is less than or equal to approximately 200 microliters. Furthermore, Applicant submits that Godowski's assay differs from Applicant's invention in that it does not teach the introduction of a ligand for associating with the biological components of interest ***intracellularly***. Godowski's invention relates to a high throughput format using immobilized cell lysates at the bottom of assay plates as the source of antigens for detection in an enzyme-linked immunosorbent assay (ELISA). In other words, Godowski teaches an assay whereby the cells are solubilized and the receptors immobilized on a second solid support prior to exposing the receptors to a ligand for detection. Applicant's screening assay relies on the introduction of the detecting ligand inside the cell where it associates with the biological component whose presence or amount is indicative of the biological or chemical process of interest. In fact, Applicant's invention has the advantage over Godowski's of preserving cellular

architecture, as well as not requiring cell lysis and subsequent lysate transfer, which are potentially rate-limiting and variable steps when dealing with large numbers of samples.

Manns was cited as teaching a standard 96 well micro-titer test plate and methods for producing the plates where the plates contain an incubation tray, a filter and a harvester tray having mating ridges and grooves to prevent cross-talk between the wells along the filter (see Abstract). Manns does not teach cell-based assays. Craig teaches methods of producing large numbers of compounds for testing against a number of biological targets.

In addition, Applicant would like to point out that the invention differs from the combination of cited references in that it teaches a cell-based screening assay wherein a ligand is contacted with the cells for binding ***intracellularly*** to biological components whose presence or amount is indicative of the intracellular biological or chemical process of interest. In addition, Applicant teaches an assay method whereby the biological component-associated ligand may be detected while still in the cell. In other words, the present invention has the advantage of not requiring cell lysis prior to detection. Furthermore, Applicant teaches a method of screening compounds that can affect post-translational events (newly added claims 104 and 105). It is generally known in the art that most cell-based assays have used reporter genes as an indicator of cellular activity (Silverman et al, "New assay technologies for high-throughput screening", *Curr. Opin. Chem. Biol.*, **2**, 397-403 (1998)), which reporter genes restrict the detection of cellular processes to transcriptional events. Also, although the changes in mRNA levels in a cell resulting from treatment with a small molecule can be used as a fingerprint, as suggested by DeRisi *et al.* (DeRisi et al, "Exploring the metabolic and genetic control on gene expression on a genomic scale", Science, 278, 680-686 (1997)), many cellular events, including post-translational events, cannot be detected with this method. Applicant teaches an assay format capable of detecting post-translational events, which can therefore be used to provide a functional profile (newly added claim 83) for each test compound, and to classify compounds functionally (*e.g.*, according to the intracellular biological processes that they affect). Applicant submits that there is no suggestion or teaching in the cited references for a method of screening compounds that can affect intracellular post-translational events using a detecting ligand that

binds to the target biological or chemical component intracellularly, nor is there any suggestion or teaching in the references to profile compounds according to the intracellular biological or chemical processes that they affect. In addition, the cited references do not teach or suggest the use of a ligand that binds to biological components intracellularly, or that ligands associated to the biological component might be detected inside the cells.

Accordingly, Applicant respectfully submits that a person of ordinary skill in the art would ***not*** have found "obvious to try" to combine the teachings of Gallop, Manns and Craig; Zambias, Manns and Craig; and/or Godowski, Manns and Craig, because there was no suggestion to combine the references, nor was there a reasonable expectation of success in the combinations in order to achieve the claimed invention. Specifically, there is no reasonable expectation of success that an intracellular product of a biological or chemical process can be detected by binding specifically to a ligand intracellularly. Applicant also submits that new claims 82-128 are not obvious over the combinations of cited references because the combinations of the cited references do not teach all of the claim limitations (*e.g.*, intracellular ligand binding and detection thereof, detection of post-translational events, functional fingerprinting). However, the present invention as described in the specification, particularly in the Examples, demonstrated experimentally that compounds ***can*** be screened for their ability to exert an effect on intracellular biological or chemical processes in high-density cell-based assay format, whereby the effect is detected via intracellular binding of a ligand with biological components characteristic of the biological process of interest.

Since there is no reasonable expectation of success in combining the teachings of Gallop, Manns and Craig; Zambias, Manns and Craig; and Godowski, Manns and Craig to achieve the claimed invention, and since the references do not teach all of the claim limitations, claims 82-128 are not obvious over Gallop, Zambias and/or Godowski in view of Manns and in view of Craig.

In light of the present Amendment and Remarks, Applicant respectfully submits that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted

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Appendix

CLAIMS AS PENDING AFTER ENTRANCE OF THE PRESENT AMENDMENT

82. A method for screening one or more test compounds to identify those that exert an effect on an intracellular biological or chemical process, the method comprising steps of:

a. introducing into each of a plurality of reaction vessels:

a plurality of cells; and

one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated;

b. introducing into each of the reaction vessels a first ligand characterized by an ability to associate intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and

c. assaying for ligand-component association in the reaction vessels.

83. A method for screening one or more test compounds; said method comprising steps of:

a. introducing into each of a plurality of reaction vessels:

a plurality of cells; and

one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated;

b. introducing into each of the reaction vessels a first ligand characterized by an ability to associate intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process;

c. assaying for association between the first ligand and the component in the reaction vessels;

d. repeating step a;

e. introducing into each of the reaction vessels a second ligand characterized by an ability to associate intracellularly with a biological component whose presence or

amount reveals the effect of a given test compound on the biological or chemical process;

f. assaying for association between the second ligand and the component in the reaction vessels;

g. optionally repeating steps d-f, wherein seconds are thirds; and

h. retaining the information as a functional fingerprint.

84. The method of claim 82 or 83 further comprising the step of removing unassociated ligand from each reaction vessel.

85. The method of claim 82 or 83 wherein the biological component is a direct participant in or a product of the biological or chemical process.

86. The method of claim 82 wherein the ligand is an antibody.

87. The method of claim 83 wherein each first, second and third ligand is independently an antibody.

88. The method of claim 86 or 87 wherein the antibody is conjugated to horseradish peroxidase.

89. The method of claim 82 wherein the method further comprises introducing a secondary ligand that binds specifically to said first ligand, and wherein the step of assaying comprises assaying for bound secondary ligand.

90. The method of claim 83 wherein the method further comprises introducing a secondary ligand that binds specifically to said first, second or third ligand, and wherein each step of assaying comprises assaying for bound secondary ligand.

91. The method of claim 89 or 90 wherein in the step of assaying, the secondary ligand is assayed intracellularly.

92. The method of claim 89 or 90 wherein the secondary ligand is an antibody.

93. The method of claim 92 wherein the antibody is conjugated to horseradish peroxidase.

94. The method of claim 82 or 89 wherein the step of assaying utilizes a detection technique selected from the group consisting of: chemiluminescence, fluorescence, phosphorescence, radioactivity, colorimetry, Ultra-Violet spectroscopy, and Infra-Red spectroscopy.

95. The method of claim 83 or 90 wherein each step of assaying independently utilizes a detection technique selected from the group consisting of: chemiluminescence, fluorescence, phosphorescence, radioactivity, colorimetry, Ultra-Violet spectroscopy, and Infra-Red spectroscopy.

96. The method of claim 82 or 83 wherein, in the step of introducing the cells in each of the plurality of reaction vessels, the cells adhere to the reaction vessel surface.

97. The method of claim 82 or 83 further comprising the step of providing one or more solutions containing at least one reagent known to exert an effect on the intracellular biological or chemical process.

98. The method of claim 97 further comprising the step of contacting the cells with the solution under suitable conditions for the reagent to exert an effect on the intracellular biological or chemical process in the cells.

99. The method of claim 98 wherein the intracellular biological or chemical process is DNA synthesis.

100. The method of claim 98 wherein the reagent is 5-bromodeoxyuridine.

101. The method of claim 82 or 83 wherein the intracellular biological or chemical process is a covalent modification of an intracellular component.

102. The method of claim 101 wherein the covalent modification is an intracellular biological reaction.

103. The method of claim 102 wherein the intracellular biological reaction is nucleic acid synthesis, protein cleavage, peptide cleavage, carbohydrate addition, carbohydrate cleavage, metabolism of cellular components, synthesis of cellular components or an intracellular biochemical reaction.

104. The method of claim 101 wherein the covalent modification is a post-translational event.

105. The method of claim 104 wherein the post-translational event is protein glycosylation, methylation, lipidation, isoprenylation, ubiquitination, phosphorylation or acetylation.

106. The method of claim 104 wherein the ligand interacts with the post-translationally modified intracellular component.

107. The method of claim 101 wherein the intracellular component is a protein.

108. The method of claim 82 or 83 wherein the cells are from the same cell –line.

109. The method of claim 82 or 83 wherein the cells are from a plurality of cell –lines.

110. The method of claim 82 or 83 wherein at least a subset of the cells comprises a eukaryotic cell.

111. The method of claim 82 or 83 wherein at least a subset of the cells comprises a mammalian cell.

112. The method of claim 82 or 83 wherein at least a subset of the cells comprises a human cell.

113. The method of claim 82 or 83 wherein the test compounds are from a natural, biological or synthetic source, or combination thereof.

114. The method of claim 82 or 83 wherein the test compounds are from a combinatorial library.

115. The method of claim 82 or 83 wherein the test compounds are covalently bound on a solid support, the method further comprising the step of dissociating the test compounds from the solid support.

116. The method of claim 82 or 83 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 200 microliters.

117. The method of claim 82 or 83 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 50 microliters.

118. The method of claim 82 or 83 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 2 microliters.

119. The method of claim 82 or 83 wherein the reaction vessels are designed to receive a volume of liquid less or equal to approximately 250 nanoliters.

120. The method of claim 82 or 83 wherein the reaction vessels are arranged with sufficient density that individual vessels are separated from one another by no more than about 5 millimeters.

121. The method of claim 82 or 83 wherein the reaction vessels are arranged with sufficient density that individual vessels are separated from one another by no more than about 2 millimeters.

122. The method of claim 82 or 83 wherein the reaction vessels are arranged with sufficient density that individual vessels are separated from one another by no more than about 1 millimeter.

123. The method of claim 82 or 83 wherein the reaction vessels are arranged with sufficient density that individual vessels are separated from one another by no more than about 0.25 millimeter.

124. The method of claim 82 or 83 wherein the number of reaction vessels is greater than or equal to approximately 384 and the reaction vessels occupy a surface smaller than or equal to approximately 128×86 mm^2.

125. The method of claim 82 or 83 wherein the number of reaction vessels is greater than or equal to approximately 1500 and the reaction vessels occupy a surface smaller than or equal to approximately 128×86 mm^2.

126. The method of claim 82 or 83 wherein the number of reaction vessels is greater than or equal to approximately 6000 and the reaction vessels occupy a surface smaller than or equal to approximately 128×86 mm^2.

127. The method of claim 82 or 83 wherein in the step of introducing the test compounds into the plurality of reaction vessels, the test compounds are the same or different.

128. The method of claim 82 or 83 wherein in the step of introducing the test compounds into the plurality of reaction vessels, each reaction vessel contains one test compound.